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REVIEW

Measles vaccination

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Measles • Prophylaxis • Immunoglobulin • Vaccine • Effectiveness

Measles virus (Rubeola)

The first written description of measles attributed to Abu Becr Rhazes in the 10th century. He referred to measles as Hasbah, which means eruption in Arabic, but the viral aetiology of measles was not confirmed until 1911 by Anderson and Golderger [1].
Measles virus is a member of the genus Morbilli virus in the family paramyxoviridae, which is a linear single strand RNA [2].
Measles is known as one of the most infections and persistent of human viral diseases. Its distribution is worldwide and it causes disease in any climate and under any condition provided that enough susceptible human beings are brought together to enable its spread [3]. Humans are the only natural host for measles virus with no animal reservoirs or vectors involved [4]. The principal mode of transmission is via droplet infection. Indirect contact and transmission by fomites may also occur. Patients are considered to be infectious from the onset of symptoms through the 4th day of rash [1], with no evidence that measles infections can occur twice [5].
In many developing countries measles is still the most important cause of death between the ages of one and five years [6].

Trends of measles

In the populous areas of the world measles causes epidemics every two to five years. Meanwhile, in the large villages and semiurban populations in the developing world epidemics occur every two to three year [7]. However, in the rapidly expanding urban conglomeration in the developing world, the continuos immigration from the original population provides a constant influx of susceptible individuals and in turn a sustained occurrence of measles and unclear epidemics. Measles in developing countries occurs at a much younger age compared with developed countries. In some area of Africa more than 50% of children may be infected before the age of two years and nearly 100% by the age of five years [1].
Countries in which measles vaccine is widely used like United States have experienced a marked decrease in the incidence of the disease. There was also concomitant shift in the age specific incidence to a higher age [8]. In developed countries measles epidemics are closely tied to the school years, building up to a peak in the late spring and ceasing abruptly after the summer has begun.
In Africa measles epidemics usually begin in the middle of the dry season and decline with the onset of the wet season. The difference in pattern from one area to another presumably is related to population dynamics and habits [7].

Measles vaccines

Numerous attempts have been made to device an effective and harmless mean for the artificial induction in man of active immunity against measles. In March of 1963 two measles vaccines were licensed for general use, live attenuated measles vaccine (Edmonston "B" type) and killed virus vaccine. The Edmonston "B" strain vaccine produced good levels of immunity but frequently caused high fever and rash about seven to ten days after immunisation [9].
By the time it was apparent that the immunogenic and protective effects of inactivated measles virus vaccine were transient. Therefore, killed vaccine was withdrawn from market in 1968 and is no longer available for use [10].
In Egypt, Hosney et al. (1964) used the killed measles virus vaccine as the first trial of measles vaccination [11]. Then Imam et al. (1965) used the live attenuated measles (Edmanston "B" strain), and since then measles vaccine has been used in Egypt [12]. Measles vaccine coverage by live attenuated vaccine (Schwarz vaccine) in Egypt had reached over 90% by year 1994 [13].
In the United States in 1971, a combined vaccine incorporating attenuated measles, mumps and rubella virus in one product was licensed and this trivalent product soon became the vaccine of choice providing with a single injection successful immunisation against all three infections. The combination showed no reduction in immunogencity or efficacy of the individual components [6].
Live attenuated measles virus vaccine is usually administrated before the age of 1 year. It is available as freeze dried preparation, stored at 4°C. This vaccine is heat and

light sensitive and this constitute the major problem. Poor storage condition results in loss of vaccine potency particularly in less developed countries where maintenance of a reliable cold chain is often difficult [14, 15].
In 1970 attention focused on the "Edmonston Zegreb" EZ vaccine produced in Yugoslavia. This vaccine possesses the potential to immunise infants successfully at a younger age [16]. Studies suggested that the "Edmonston Zegreb" EZ vaccine given at 4-6 months may provide more protection than the Schwarz vaccine given at 9 months [17, 18].

Measles vaccination policy

Measles maternal antibody persists in the infant for most of the first year of life. This antibody interferes with the response to measles vaccine. Clearly then it is better to delay vaccination until after the end of the first year. In developing countries where measles is endemic, the recommended age of measles vaccination has been estimated at 9 months. At this age measles maternal antibody has usually fallen to low level and vaccination of infants may give a seroconversion rate of 80% [3, 19-22].
In Egypt, the Expanded Programme of Immunization first recommended a single dose of live attenuated vaccine (Schwarz vaccine) at the age of 9 months [13]. In 1997 a retrospective case control study in two primary schools located in Cairo was conducted to evaluate the protective value of routine measles vaccination. The overall measles vaccine effectiveness was estimated at 53% (95% CI 71%-26%), and there was an association between age of measles vaccination and vaccine effectiveness. Vaccination failure due to young age of measles vaccination was the likely explanation of the low measles vaccine effectiveness. This study recommended the adoption of two-dose measles vaccination policy with the second dose being given at older age [23]. The Expanded Programme of Immunization of Egypt 2 years later recommended a second dose of Schwarz vaccine at the age of 18 months [24].
Until 20 years ago, in the developed world, measles vaccine was given to children in their second year after the age of 15 months [25] as one dose, but Sweden and Finland has already given a second dose several years after the first [26].
USA has adopted a two-dose policy and this strategy was the recommendation of the 1989 Meeting National Program Managers to all European Member States. The rationale for a two-dose policy is to assure the highest possible level of immunity [27]. This recommendation matches with results obtained following an outbreak of measles in a primary school in the Australian capital territory in September 1993 where there was no increased risk of measles infection in those who had been immunised under 15 months of age compared with those immunised at 15 months or older. Also none of the children who had received two-dose of vaccine caught measles [28].
Following a large measles outbreak during 1992 in Oman with total of 562 cases the out-line immunisation schedule was modified into two doses of measles vaccine; a dose of signal antigen measles vaccine at 9 months, and a dose of MR (Measles, Rubella) vaccine at 15 months [29].
In United Arab Emirates the plan of action for the elimination of indigenous transmission of measles includes the administration of 2 doses of measles vaccine in the routine schedule at 9 months and 15 months of age and emphasises the importance of increasing the immunisation coverage to a level that exceeds 95% of all infants [30].

Effectiveness of measles vaccine

Similar to immunity after natural infection, live measles vaccine induced immunity has been thought to be life long [14, 31]. Reyes (1987) reported that seroconversion is an indicator of measles vaccine efficacy. Failure to seroconvert could be due to *primary vaccine failure* which is generally attributed to neutralisation of the attenuated vaccine virus by persistent maternal antibody in infants younger than 12 months of age or to inadequate immunisation as a consequence of bad storage conditions and handling or *secondary vaccine failure* which refers to the development of clinically apparent measles infection despite an immune response to initial vaccination. The elected response may be inadequate to protect against the subsequent inoculum of wild type virus or an initially protective response may wane over time [32].
Vaccine efficacy tells us what proportion of children is protected by immunisation against a disease. Measles vaccine under ideal condition has a high efficacy (about 90%). According to WHO 1989 reports, a vaccine efficacy of 90% means that your program is as effectively as possible. Vaccine efficacy of 80- 90% means that your program is not as effective as it could be, but there is not a major problem.Vaccine efficacy of less than 80% indicates that there is a problem with the program. This could be due to problem with the cold chain, the injection technique, or the age at which health workers are immunising children, and you should take action to correct it [33].
WHO Global Advisory Group (1990) had recommended primary vaccination to be at the age of nine months in endemic areas to avoid infection at young age [34]. This policy also has caused major reductions in incidence of measles and its complications but has failed to eradicate the disease even in developed countries [22, 35].
In a previous study conducted in Egypt by Khashaba (1993), measles antibody titres were shown to decrease gradually as time passes after vaccination, but it was still protective at age 10-12 years. For those who shown a low titre primary rather than secondary vaccine failure appears to be responsible for the high failure rate in Egypt [36]. This problem continued till changing the

vaccine calendar with the administration of a second dose at the age of 18 months [24].

Low vaccine effectiveness in developing countries has usually been explained in terms of either too young an age at vaccination or a poor cold chain [18].

Age of vaccination is considered as the most important factor in measles vaccine effectiveness. Effectiveness increased from 84% at age 9 months to 100% at 12 months in Haiti. Similarly, Effectiveness is from 92.5% at 9 months to 100% at 12 months in Kenya [37].

Following a large measles outbreak in Quebec City in 1989, a school-based case-control study was conducted to evaluate measles vaccine effectiveness with respect to age at vaccination. The relative risks of measles and the results showed a trend towards increased vaccine efficacy with increasing age at vaccination ($P < 0.001$). Vaccine efficacy elevated from 85% in children vaccinated at 12 months of age to equal to or more than 94% in those vaccinated at 15 months and older [38].

Similarly in Ivory Coast vaccine effectiveness was found to be as low as 56% for children immunised around 9 months to a high of 100% among children immunised at 15 months or older [39].

In Brazil, vaccine efficacy was only 43% for children who received the vaccine around 9 months of age, against 83% for those who were immunised later [40].

In N'Djamena, capital of Chad, measles vaccine efficacy was estimated by comparing attack rates in unvaccinated and vaccinated children. The result was 71% (95% CI: 59-80%) for children vaccinated with a single dose of Schwarz vaccine at age 9 months [41].

A lower figure of 54% (95% CI, 36%-67%) was estimated in Dar El Salaam, Tanzania following a case-control study for evaluating the protective effect of measles vaccine under routine vaccination at 9 months of age [42]. Similarly the measles elimination campaign in the Caribbean recommended that measles vaccine should be administrated at 12 months instead of 9 months. This would maximise the efficacy but should only be done if the attack rate of measles is very low [43].

Low vaccine effectiveness could be explained by the presence of maternal antibodies against measles in infants up to 9 months of age. These antibodies interfere with the seroconversion to measles vaccine [19].

In Kinshasa, Zaire, vaccination at age 6 months with "Edmonston-Zagreb" EZ vaccine was introduced in 1989. This vaccine achieved over 90% reduction in reported measles incidence, with a fall in the proportion of cases less than 9 months of age. However, this could be attributed to concomitant high coverage with this vaccine [44].

In Egypt the age of primary vaccination tended to be at the age of 9 months with no booster and this has been shown to cause decreased vaccine efficacy. Such findings draw the attention for the importance of a booster dose to assure the highest possible level of immunity [20, 23].

Primary vaccine failure normally occurs in 2-5% of recipients of a single dose measles vaccine, and this percentage may be enough to sustain transmission. It is anticipated that the second dose will protect 95-98% of those who remain susceptible after the first dose [45].

Khashaba et al. (1988) concluded that vaccination before one year resulted in a significantly lower mean antibody titres when compared to infants vaccinated at age 15 months or later. However, demonstrable antibody titres were evident in 15% of the older studied infants indicating prior infection. It was therefor recommended to give a primary vaccine at 9 months to protect against measles infection and to administer a subsequent booster to ensure higher antibody titres and high seroconversion rates [36].

This agrees with the recommendations of the Department of Health in Australia that announced a two doses schedule [45].

Such policy proved successful following an outbreak of measles in Australia where none of the children who had received two-dose of vaccine caught measles [28].

In Canada, despite that vaccine coverage had reached 99.7% with one dose of measles vaccine an outbreak had occurred among secondary school children. This emphasised that similar outbreaks could happen any where with current routine one dose schedule. The National Advisory Committee of Immunisation recommended a second booster dose to avoid such outbreaks [30].

The Centres for Disease Control and Prevention of USA (2001), recommended vaccination at 6 months of age followed by routine revaccination when exposure of infants to measles is likely, especially in areas at high risk. Early two-dose measles vaccination was associated with improved coverage and a comparably high level of humoral immunity and clinical protection as a single dose at age ≥ 12 months [46].

The WHO European Region has a measles elimination target for 2010. Between September 2005 and mid-June 2006, more than 50,000 measles cases were reported in Ukraine; many reportedly had received two doses of measles vaccine and over 60% were among persons 15-29 years old. To investigate vaccine effectiveness, a case-control study was undertaken in Dnepropetrovsk region. Vaccine effectiveness for two doses of measles vaccine was 93.1%, providing insufficient population immunity for measles elimination. An additional dose of measles vaccine for these age-cohorts was recommended required if Ukraine is to achieve measles elimination [47].

So et al. (2008) reported a measles outbreak in a preschool in Incheon (Korea). The epidemiological investigation of this outbreak showed that the vaccine's efficacy was 88.8% in the one dose group and 98.0% in the two doses group. The authors recommended improving the coverage with two doses vaccination [48].

In 2006, a large measles outbreak (number = 614) occurred in Duisburg city, Germany, with 54% of cases aged > 9 years. An investigation was launched to determine reasons for the resurgence of measles, assess vaccination coverage and vaccine effectiveness. The results showed vaccine effectiveness of 98.1% (95% CI: 92-100%) in students with one and 99.4% (95% CI: 97-100%) with two measles containing vaccine doses [49].

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